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FOLEY & LARDNER LLP
P.O. BOX 80278
SAN DIEGO, CA 92138-0278

EXAMINER	
JOHANNSEN, DIANA B	
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1634	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/615,497	HUANG, DOUG HUI	
	Examiner	Art Unit	
	Diana B. Johannsen	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 November 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,4-18,30-32,36 and 39-50* is/are pending in the application.

4a) Of the above claim(s) *36,39-45 and 47-50* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,4-18,30-32 and 46* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Applicant's election without traverse of the primer combination of Group (a), SEQ ID NOS 1-4, in the Reply and Amendment filed on November 24, 2008 is acknowledged. Applicant's prior election of the polymorphisms CYP2D6*4, CYP2D6*5, and CYP2D6*Nx2 (and corresponding phenotypes) and of corresponding primers SEQ ID Nos 9, 14, and 11 in the reply filed on May 9, 2006 is also again noted (see also the Office action of November 1, 2006).

2. It is noted that applicant's Reply and Amendment of November 24, 2008 also added new claims 49-50 dependent from claim 1, and requiring that a cytochrome P450 2D6 gene sequence be "further amplified using multiplex amplification primers comprising SEQ ID NOs: 5-8", such that the claims encompass, e.g., separate and different method steps employing SEQ ID NOS 1-4 and SEQ ID NOS 5-8, as well as the use of the primers together in a single step. Claims 49-50 encompass a species that differs both structurally and functionally from the species (a) and (b) recited in the Election/Restriction of July 22, 2008, and require a different search and consideration of different issues under 35 USC 112, first paragraph as compared to species (a) and (b). Accordingly, the species of claims 49-50 would have been treated as a separate species (c), for the same reasons given in the Election/Restriction of July 22, 2008, had these claims been pending at the time that Election/Restriction requirement was made. Additionally, it is noted that while species (a) and (b) constitute subcombinations usable together (as evidenced by species (c) in claims 49-50), applicant's separate recitation of

species (a) and (b) constitutes evidence that these subcombinations are each separately usable (see MPEP 806.05(d)). Accordingly, claims 49-50 are withdrawn from consideration as being drawn to a non-elected species.

3. Claims 36, 39-45, and 47-50, as well as claims 9-10, 30-32 and 46 in part (to the extent drawn to non-elected species), are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected species, there being no allowable generic or linking claim. With regard to the separation of species (a) and (b), election was made **without** traverse in the reply filed on November 24, 2008.

Specification

4. The substitute specification filed April 30, 2008 has not been entered because it does not conform to 37 CFR 1.125(b) and (c) because: it does not properly illustrate all changes relative to the immediate prior version of the specification. In particular, it appears that applicant has not taken into account the prior amendments to the specification of December 17, 2003 and May 1, 2007.

5. In accordance with MPEP 714.20, the substitute specification of April 30, 2008 has been denied entry; however, the claim amendments and response of April 30, 2008 and November 24, 2008 have been entered and considered.

Claim Rejections - 35 USC § 112, second paragraph

6. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

7. Claims 1, 4-18, 30-32 and 46 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1, 4-18, 30-32 and 46 are indefinite over the recitation of the limitation "step (a)" in claim 1 because the claim does not previously employ the term “step” or otherwise identify item (a) as a “step”. Thus, it is not clear how the reference to “step (a)” limits the claims, and there is insufficient antecedent basis for the limitation “the gene sequence amplified in step (a)”.

Claims 1, 4-18, 30-32 and 46 are indefinite because it is unclear whether the claims are directed to methods of identifying ‘at least one” polymorphism, as indicated in the preamble of claim 1, or merely a single polymorphism, as indicated in the body (item (b)) of the claim. It is noted that some dependent claims (claims 8, 12-17) reference “said…polymorphism”, suggesting that the claims are limited to the detection of one polymorphism, while others (claims 9-10) reference "said at least one of...polymorphisms," suggesting that the claims embrace detection of one or more polymorphisms. Accordingly, the claims should be amended such that they are clear and consistent.

Claims 4-5 are indefinite over the recitation of the limitation "step (b)" in claim 4 because the claims do not previously employ the term “step” or otherwise identify item (b) of claim 1 as a “step”. Thus, it is not clear how the reference to “step (b)” limits the claims. Additionally, there is insufficient antecedent basis for the recitation “said at least

one labeled nucleic acid" in claim 4, as such a nucleic acid is not previously referenced in the claims.

Claim 6 is indefinite over the recitation of the limitation "steps (a) or (b)" in claim 6 because the claims do not previously employ the term "step" or otherwise identify items (a) and/or (b) of claim 1 as "steps". Thus, it is not clear how the reference to "steps (a) or (b)" limits the claims.

Claim 18 is indefinite because it is unclear how the claim further limits claim 1, from which it depends. Particularly, claim 18 is drawn to the method of claim 1 "further comprising detection of wildtype P450 2D6". However, claim 1 is drawn to a method of identifying the presence or absence of a P450 2D6 polymorphism comprising a step of amplifying followed by a step of polymorphism identification. It is not clear how detection of wildtype P450 2D6 relates to or further limits the method of claim 18. For example, is claim 18 intended to require "identifying" the absence of a polymorphism in the 2D6 gene of the sample referenced in claim 1, or, e.g., an additional method step of detecting a control wild type 2D6 sequence? Because the relationship between the "detection" of claim 18 and the method of claim 1 is not made clear by applicant's claim language, clarification is required.

Claim Rejections - 35 USC § 103

8. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

9. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

10. Claims 1, 4, 6-9, 11-18, 30-32 and 46 are rejected under 35 U.S.C. 103(a) as being unpatentable over Anastasio et al (WO 02/38589 A2 [05/16/2002; filed 11/09/2001]) in view of Stuven et al (Pharmacogenetics 6:417-421 [1996]; cite no. A69 of the IDS of 02/2004) and Steen et al (Pharmacogenetics 5:215-223 [1995]), as evidenced by Goelet et al (WO 92/15712 [09/17/1992]).

The claims are drawn to a method of "identifying the presence or absence of at least one cytochrome P450 2D6 polymorphism in a sample" comprising "amplifying a cytochrome P450 2D6 gene sequence from the sample using multiplex amplification primers comprising SEQ ID NOs: 1-4" and "identifying the presence or absence of a cytochrome P450 2D6 polymorphism in the gene sequence amplified in step (a) using a primer extension reaction comprising a plurality of extension primers and a set of distinctively labeled ddNTPs" (see text of independent claim 1).

It is noted that the portions of the Anastasio et al reference on which the instant rejection relies find support in provisional application 60/247,943, filed November 9, 2000.

Anastasio et al disclose methods of genotyping and haplotyping the CYP2D6 gene in which one or more of the polymorphisms present in the gene are detected (see entire reference). Anastasio et al disclose methods in which primer extension is employed to identify polymorphisms, and disclose "primer extension oligonucleotides" for use in their methods in which the 3' termini of the oligonucleotides are "complementary to the nucleotide located immediately adjacent to the polymorphism site" (see, e.g., pages 18 and 22-23, and claim 4). In these methods of Anastasio et al, isolated nucleic acids from an individual are amplified, and primer extension is performed on the amplified nucleic acids, wherein the identity of the terminator in the extended oligonucleotide is identified to determine the identity of the polymorphism(s) present (see, e.g., page 22 and claim 4). While Anastasio et al do not refer to the use of "distinctively labeled ddNTPs" in their methods (as set forth in independent claim 1), Anastasio et al do disclose the use of the "polymerase-mediated primer extension method" of patent WO92/15712 (Goelet et al) in the identification of polymorphisms (page 23). Goelet et al teach that their method employs differently labeled terminators, such that the identification of the nucleotide at the position of interest may be established based on the identity of the detectable marker incorporated into the primer during extension (see entire reference, particularly pages 10-13 and 21-22, summarizing the primer extension method of Goelet et al). Thus, the Goelet et al

reference provides extrinsic evidence that the primer extension method of Anastasio et al involves the use of "a set of distinctively labeled ddNTPs" as required by the claims.

It is further noted that Anastasio et al disclose the practice of primer extension assays on arrays in order to detect multiple polymorphisms "at the same time" (see page 19), as well as the use of sets of primer pairs to assay multiple polymorphic sites by primer extension (see page 22), and the investigation of "multiple polymorphic sites…simultaneously" (page 23). Further, Goelet et al disclose that primer extension involves the use of 4 differently labeled ddNTPs (see page 11), and also provide teachings of how primer extension may be performed to analyze "one or more specified positions" wherein "different positions can be determined simultaneously" (see, page 12, as well as pages 31-33). However, Anastasio et al as evidenced by Goelet et al do not teach amplifying "using multiplex amplification primers comprising SEQ ID NOs: 1-4," as required by the claims.

Like Anastasio et al, Stuven et al teach methods for detecting multiple CYP2D6 gene polymorphisms/alleles (see entire reference). Stuven et al disclose the use in their methods of a step of long distance PCR for amplification of the entire CYP2D6 gene, thereby providing a template usable in the simultaneous detection of multiple different polymorphisms (see entire reference, particularly the abstract and page 418). The primer pair employed in this long distance PCR is identical to the primer pair identified in the instant application as SEQ ID NOS 1-2 (see page 418, Table 1, the "preamplification" primers "P 1-5" and "n"). In view of the teachings of Stuven et al, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the

invention was made to have modified the method of Anastasio et al so as to have employed therein a step of preamplification with the primers of instant SEQ ID NOS 1 and 2. An ordinary artisan would have been motivated to have made such a modification because Stuven et al specifically teach that such an amplification provides a convenient template for CYP2D6 genotyping, said template encompassing multiple polymorphisms that one analyzing the CYP2D6 genotyping would wish to detect.

Additionally, Stuven et al further disclose that the null allele CYP2D6*5 causes a poor metabolizer phenotype for CYP2D6 (see pages 417-418, left column), and suggest using the CYP2D6*5 detection method of Steen et al in combination with methods directed at detecting other genotypes to obtain "comprehensive genotype" information (page 421, left column). A review of the Steen et al reference reveals that the method suggested by Stuven et al is a PCR based detection method that employs primers identical to instant SEQ ID NOS 3-4 (see the entire Steen et al reference, particularly the right column of page 217, the primers identified as "CYP-13" and "CYP-24"). In view of the teachings of Stuven et al and Steen et al, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have further modified the method suggested by Anastasio et al in view of Stuven et al so as to have included therein an amplification employing the primers taught by Steen et al (i.e., instant SEQ ID NOS 3-4) directed at identification of the CYP2D6*5 null allele, and thereby to have performed a method meeting all the requirements of the claimed invention. An ordinary artisan would have been motivated to have made such a modification because Stuven et al specifically suggest including such a reaction to allow

for identification of CYP2D6*5 to achieve "comprehensive" genotyping of CYP2D6. It is noted that instant claim 1 employs the term "multiplex amplification primers" in referring to SEQ ID NOS 1-4; however, the cited references teach the exact primers required by the claim, and meet the requirements of the claims as written. Particularly, it is noted that the claims as written do not in fact require, e.g., that all 4 primers be employed in a single tube or other container when performing the "amplifying" step of the claims; rather, the claims merely require "amplifying…from the sample" using the primers.

Regarding dependent claim 4, it is again noted that claim 1 does not reference an "at least one labeled nucleic acid" (or a "step (b)"). However, to the extent that the claim is drawn to a method actually requiring electrophoresis of a labeled nucleic acid, it is noted that the method of Goelet et al (i.e., the method relied upon by the Anastasio et al reference) requires identification of the detectable marker present on the terminator incorporated during primer extension (see, e.g., pages 11 and 22), and Goelet et al teach subjecting labeled, extended primers to polyacrylamide gel electrophoresis (see, e.g., page 38 and 43), such that the technique employed by Anastasio et al encompasses electrophoresis of a labeled nucleic acid.

With respect to claim 6, Goelet et al also disclose automated methods (see, e.g., page 51-52).

Regarding claim 7, Goelet et al disclose the labeling of each terminator with a different fluorophore (see, e.g., page 20).

Regarding claims 8-9, 18, 32, and 46, Anastasio et al disclose more than 40 polymorphisms of the CYP2D6 gene, including multiple polymorphisms encompassed

by the claims, and disclose detection of numerous haplotypes/genotypes of CYP2D6, including the wild type gene (see entire reference). With regard to the polymorphisms elected by applicant, it is particularly noted that the polymorphism identified by Anastasio et al as "PS33" corresponds to CYP2D6*4 (see, e.g., page 4 and Figure 1B). It is also again noted that Stuven et al suggest detection of CYP2D6*5 by the method of Steen et al.

Regarding claims 12-17, 30-32, and 46, Anastasio et al disclose that CYP2D6 is a "pharmaceutically-important" gene whose gene product is involved in metabolism of a variety of drugs including "antiarythmics, adrenoceptor antagonists, and trycyclic antidepressants," and teach that CYP2D6 genotype affects the extent to which a variety of drugs are metabolized in subjects (see, e.g., pages 1-3). With further regard to claims 30-32 and 46, Anastasio et al also teach the use of their genotyping/haplotyping methods in selecting appropriate drugs for treatment of a disease or condition (see, e.g., pages 7, 26-27), and therefore the teachings of Anastasio et al in view of Stuven et al and Steen et al suggest the methods of the claims.

Regarding claim 11, it is noted that the samples disclosed by Anastasio et al are human samples (see entire reference, particularly, e.g., the examples).

11. Claim 5 is rejected under 35 U.S.C. 103(a) as being unpatentable over Anastasio et al in view of Stuven et al and Steen et al, as evidenced by Goelet et al, as applied to claims 1, 4, 6-9, 11-18, 30-32 and 46, above, and further in view of Dovichi and Zhang (Methods in Molecular Biology 167:225-239 [2001]; cite no. A20 of the IDS of 02/2004).

It is again noted that while the claims do not clearly require an "at least one labeled nucleic acid" or a "step (b)", the teachings of Anastasio et al, Stuven et al, and Steen et al, as evidenced by Goelet et al, do teach identification of the terminator incorporated during primer extension by electrophoresis of a labeled nucleic acid. However, these references do not teach the use of capillary electrophoresis, as required by claim 5.

Dovichi and Zhang teach that capillary electrophoresis (CE) allows for the more rapid determination of a DNA sequence as compared to conventional polyacrylamide gel electrophoresis (PAGE)(see entire reference, particularly pages 227-228). In view of the teachings of Dovichi and Zhang, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Anastasio et al in view of Stuven et al and Steen et al, as evidenced by Goelet et al, so as to have subjected extended primers to CE rather than PAGE. An ordinary artisan would have been motivated to have made such a modification for the advantage of more rapidly determining the terminal base present in extended primers, as suggested by the teachings of Dovichi and Zhang.

12. Claim 10 is rejected under 35 U.S.C. 103(a) as being unpatentable over Anastasio et al in view of Stuven et al and Steen et al, as evidenced by Goelet et al, as applied to claims 1, 4, 6-9, 11-18, 30-32 and 46, above, and further in view of Pastinen et al (PCR Applications (1999), pages 521-535; Innis, M.A. et al, editors, Academic Press, San Diego).

Anastasio et al, Stuven et al, and Steen et al, as evidenced by Goelet et al, do not teach an extension primer having any of SEQ ID Nos 9-19, as required by the claim. It is again noted that Applicant has elected SEQ ID Nos 9, 11, and 14 for examination.

Pastinen et al disclose a method of genotyping the CYP2D6 gene that accomplishes detection of multiple CYP2D6 alleles, including the elected CYP2D6*4 allele, by primer extension (see entire reference, particularly pages 529-530). The primer employed by Pastinen et al in detection of the CYP2D6*4 allele, primer 2D6*4 (see page 530), comprises the sequence identified by applicant as SEQ ID NO: 9.

In view of the teachings of Pastinen et al, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have modified the method suggested by Anastasio et al in view of Stuven et al and Steen et al, as evidenced by Goelet et al, so as to have employed therein the 2D6*4 primer of Pastinen in the detection of the CYP2D6*4 allele of the CYP2D6 gene. As Anastasio et al, Stuven et al and/or Steen et al do not exemplify detection of this allele using primer extension, and as Pastinen et al exemplify the successful use of their primer in detection of the CYP2D6*4 allele, an ordinary artisan would have been motivated to have made such a modification (as opposed to, e.g., experimenting with various primers in order to identify an appropriate primer) for the advantage of more rapidly and conveniently achieving detection of the CYP2D6*4 allele.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Diana B. Johannsen whose telephone number is

571/272-0744. The examiner can normally be reached on Monday and Thursday, 7:30 am-4:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached at 571/272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Diana B. Johannsen/
Primary Examiner, Art Unit 1634